

Variant: *NM_030662.3(MAP2K2):c.692G>T (p.Arg231Leu)*

Version: 1.0

CA296133 [↗](#)

40818 (ClinVar) [↗](#)

Gene: MAP2K2 ([HGNC:5605](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: c77c7f8b-de11-4d2a-b1e3-d7190a41ba9f

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HGVS expressions

NM_030662.3:c.692G>T

NM_030662.3(MAP2K2):c.692G>T (p.Arg231Leu)

NC_000019.10:g.4101032C>A

CM000681.2:g.4101032C>A

NC_000019.9:g.4101030C>A

CM000681.1:g.4101030C>A

NC_000019.8:g.4052030C>A

NG_007996.1:g.28097G>T

ENST00000262948.9:c.692G>T

ENST00000394867.8:c.401G>T

ENST00000593364.5:n.639G>T

ENST00000597008.5:n.293G>T

ENST00000597263.5:n.156G>T

ENST00000599021.1:n.16G>T

ENST00000601786.5:n.993G>T

ENST00000602167.5:n.412G>T

Uncertain Significance

Met criteria codes **4**

PS4_Supporting PP2 PP3 PM2

Not Met criteria codes **19**

BS2 BS1 BS4 BS3 BP4 BP3
BP1 BP2 BP5 BP7 BA1 PS1
PS2 PS3 PP1 PM6 PM1
PM5 PM4

Evidence Links **0**

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.692G>T (p.Arg231Leu) variant has been identified in at least 2 independent occurrences in patients with clinical features of RASopathies (PS4_Supporting GeneDx, Invitae internal data, GTR Lab IDs 26957, 500031; ClinVar SCV000207960.9, SCV000551455.2). This

variant was absent from large population studies (PM2; gnomAD, <http://gnomad.broadinstitute.org>). The variant is located in the MAP2K2 gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2; PMID: 29493581). Computational prediction tools and conservation analysis suggest that the p.Arg231Leu variant may impact the protein (PP3).In summary, the clinical significance of the p.Arg231Leu variant is uncertain. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PS4_Supporting, PM2, PP2, PP3.

Met criteria codes

PS4_Supporting			This variant was observed in 2 patients at GeneDx (one without clinical information and one with clincial diagnosis of NSML) Invitae: observed MAP2K2 p.Arg231Leu once, in patient with features of NSML. It was absent from ExAC/gnomAD and the predictors were all deleterious. We have not tested any additional family members. These two NSML occurrences make the variant meet PS4_Supporting, despite MAP2K2 not having a lot of information to associate it with NSML
PP2			The variant is located in the MAP2K2 gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2; PMID: 29493581).
PP3			Computational prediction tools and conservation analysis suggest that the p.Arg231Leu variant may impact the protein (PP3).
PM2			This variant is absent in gnomAD.

Not Met criteria codes

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			Neither report seems to indicate that these occurrences were de novo
PM1			aa 47-65, 128-138 are the regions defined by the RAS VCEP for MAP2K2
PM5			Variant at same codon as the NM_030662.3(MAP2K2):c.692G>A (p.Arg231His) variant in ClinVar which will also need to be assessed.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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